*THIS OPINION WAS NOT WRITTEN FOR PUBLICATION*

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 18

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* LISA S. BEAVERS,
THOMAS F. BUMOL and
ROBERT A. GADSKI

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Appeal No. 93-3731
Application 07/387,665[1]

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ON BRIEF

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Before McKELVEY, *Chief Administrative Patent Judge*, WINTERS and ELLIS, *Administrative Patent Judges*.

ELLIS, *Administrative Patent Judge*.

*DECISION ON APPEAL*

This appeal is from the final rejection of claims 1-36, which are all the claims pending in the application.

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[1] Application for patent filed July 31, 1989.

Claims 1 and 17 are illustrative of the subject matter on appeal and are attached as an appendix to this decision.

In setting forth the statement of rejection in the Answer, the examiner relies on the following references:

Cabilly et al. (Cabilly) 4,816,567 Mar. 28, 1989

Bumol et al. (Bumol (PNAS)), "Unique glycoprotein-proteoglycan complex defined by monoclonal antibody on human melanoma cells," 79 *Proc. Natl. Acad. Sci.* 1245-1249 (1982).

Bumol et al. (Bumol (JBC)), "Biosynthetic Studies of Proteoglycans in Human Melanoma Cells with a Monoclonal Antibody to a Core Glycoprotein of Chondroitin Sulfate Proteoglycans," 259 *J. Biol. Chem.* no. 20, 12733-12741 (1984).

Elsewhere in the Answer, the examiner refers to these references:

Lewis, Jr. et al. (Lewis) 4,533,496 Aug. 6, 1985

Suggs et al. (Suggs), "Use of synthetic oligonucleotides as hybridization probes: Isolation of cloned cDNA sequences for human $\beta_2$-microglobulin," 78 *Proc. Natl. Acad. Sci.* no. 11 6613-6617 (1981).

Morgan, Jr. et al. (Morgan), "Monoclonal Antibodies to Human Melanoma-associated Antigens: An Amplified Enzyme-linked Immunosorbent Assay for the Detection of Antigen, Antibody, and Immune Complexes," 43 *Cancer Research* 3155-3159 (1983).

Schroff et al. (Schroff), "Monoclonal Antibody Therapy in Malignant Melanoma: Factors Effecting In Vivo Localization," 6 *J. Biol. Response Mod.* no. 4, 457-472 (1987).

Morrison, "IN VITRO ANTIBODIES: Strategies for Production and Application," 10 *Annu. Rev. Immunol.* 239-265 (1992).

Claims 1-36 stand rejected under 35 U.S.C. § 103 as unpatentable over Cabilly in view of either Bumol (PNAS) or Bumol (JBC). We reverse.

**Background**

The present invention is directed to a DNA molecule which encodes a chimeric antibody comprising (i) a light or heavy chain variable region derived from a murine hybridoma specific for a glycoprotein found on the surface of all human melanoma cells, and (ii) a constant region derived from a human lymphocyte. Using recombinant DNA techniques, the appellants have determined the DNA sequence of the entire coding sequence of the light and heavy chains of a murine monoclonal antibody, 9.2.27, which is specific for the core protein of chondroitin sulphate proteoglycan (CSP) found on the surface of melanoma cells. They disclose that the portion of the DNA which encodes the light and heavy chain variable regions of the monoclonal antibody can be ligated to DNA encoding the respective light and heavy chain constant regions derived from a human antibody. The resultant chimeric DNA constructs are inserted into an expression vector and used to transfect, in a sequential manner, an eucaryotic host cell. Alternatively, the chimeric DNA sequences can be combined into a single expression vector prior to transfection or transformation.

Cabilly discloses the construction of chimeric antibodies, in general, wherein the DNA sequences which encode the relevant portions of an antibody of interest are inserted into an expression vector and used to transform a suitable eucaryotic host cell. Specifically, Cabilly teaches the construction of chimeric antibodies comprising the variable region of a murine monoclonal antibody directed against the human carcinoembryonic antigen (CEA) and the human $\gamma$-2 constant region using recombinant DNA techniques.

Bumol '82 describes the isolation of a murine monoclonal antibody directed against a 250 kD glycoprotein (CSP) which is present on the surface of all human melanoma cell lines; i.e., monoclonal antibody 9.2.27. Bumol '84 describes the use of the monoclonal antibody 9.2.27 as a probe in biosynthetic studies for the characterization of CSP. The Bumol references do not disclose the amino acid or nucleotide sequence of the monoclonal antibody or suggest its use in the formation of a chimeric antibody.

**Opinion**

We have carefully considered the respective positions of the appellants and the examiner and find ourselves in substantial agreement with that of the appellants.

The examiner has argued that in view of the teachings of the applied prior art it "would have been *prima facie* obvious to one of ordinary skill in the art to deduce the DNA sequence of the variable region of the antibody [monoclonal antibody 9.2.27] and to ligate this DNA to an expression vector which would be capable of transforming a host cell in order to make large quantities of the recombinant antibody specific for the melanoma CSP."[2] The examiner has acknowledged that the cited prior art does not teach the DNA sequence of monoclonal antibody 9.2.27; however, he has urged that "obtaining the amino acid sequence and the DNA sequence of a known protein was well known and taught in the art at the time the invention was made."[3] The examiner has cited a publication by Suggs, PNAS, vol. 78, pp. 6613-6617 (1981), which was not included in the statement of his rejection, to support this position. The examiner then proceeded to recite various known techniques, one after the other, in order to establish the feasibility of making a DNA sequence which encodes a chimeric antibody as required by the claims. Finally, he has concluded that one skilled in the art "would have been motivated to make the chimeric antibodies of the instant invention" in view

[2] The examiner's answer, p. 4, lines 13-18.

[3] *Ibid.*, p. 4, lines 10-13.

of the teaching of Schroff (Journal of Biological Response Modifiers, vol. 6, pp. 457-572 (1987)) that the monoclonal antibody 9.2.27 "was useful for *in vivo* diagnostics and furthermore because it was known in the art that murine antibodies have characteristics which may severely limit their use in human therapy or diagnosis."[4] As with the Suggs reference, the Schroff reference was not included in the statement of rejection. The examiner has also embellished his statement of motivation by enumerating several problems which can occur when murine antibodies are employed for human therapeutic purposes and the desirability of using chimeric antibodies. We find this position untenable.

Turning first to the citations of the Suggs and Schroff references in the body of the rejection, we find the examiner's reliance on these publications inappropriate. It is well established that "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of the rejection." *In re Hoch*, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970). Therefore, we have not considered

[4] *Ibid.*, p. 3, lines 26-32.

these references in our deliberations and have based our decision solely on the teachings of the Cabilly and two Bumol publications. Similarly, we have not considered the additional references listed on p. 2 of this decision.

As delineated in the Appellants' Brief, the examiner has the initial burden of establishing that (i) the teachings of the cited prior art would have suggested to those of ordinary skill that they should make the claimed compositions, and (ii) such persons would have a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). This suggestion must be in the prior art and not in the appellants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 4691, 5 USPQ2d 1529 (Fed. Cir. 1988). In the case before us, however, we find that the examiner has disregarded both of these requirements for making a *prima facie* case of obviousness.

First, we find from a fair reading of the references, that they fail to provide any teachings or suggestion to make the present DNA sequences. The Bumol publications teach the construction of murine monoclonal antibody 9.2.27 and the use of said monoclonal to study the biosynthesis of the CSP in melanoma cells. There are (i) no teachings as to the DNA (or amino acid) sequence of the monoclonal, (ii) no suggestion to obtain this information, and (iii) no suggestion that if the

portion of the DNA sequence which encodes the variable region of the monoclonal antibody 9.2.27 were available, that it should be ligated to a DNA sequence derived from a human lymphocyte which encodes the constant region of an antibody in order to make a DNA sequence encoding a chimeric antibody.

We are cognizant of the fact that the examiner did not rely on the Bumol references alone, and that he applied these references in combination with the Cabilly publication. It is well understood that the test of obviousness is not the express suggestion of the claimed invention in any one reference, but what the collective teachings of the references would have suggested to one of ordinary skill in the art at the time the application was filed. *In re Betz*, 418 F.2d 942, 163 USPQ 691 (CCPA 1969).

However, we do not find that the teachings of Cabilly redress the basic deficiencies of Bumol. As we noted, *supra*, the Cabilly patent describes the art-recognized techniques in molecular biology which can be employed to make DNA molecules which encode chimeric antibodies in general, including *inter alia*, chimeric antibodies comprising the variable region derived from one mammalian species and the constant region from a different species. In our opinion, such a disclosure

describes a possible avenue of research which can be pursued, presuming one has characterized a particular monoclonal antibody at the DNA level. In the present case, neither the DNA or amino acid sequences of the monoclonal antibody 9.2.27 were available or suggested, by any means or in any form, in the Bumol references. Therefore, the teachings of Cabilly as to constructs which can be made with the DNA sequence of a mammalian antibody do not fairly suggest obtaining the 9.2.27 DNA sequence and using only that portion which encodes the variable region, to construct a DNA molecule with encodes a chimeric antibody. Accordingly, we do not find a teaching that it is possible to make a DNA sequence encoding a chimeric antibody comprising a variable region derived from one species and a constant region derived from another, or even murine variable and human constant region, in combination with the teachings of Bumol to be suggestive of the present DNA sequences.

Having determined that the applied references fail to teach or suggest the present invention, it is not necessary for us to determine whether or not the examiner has complied with the second requirement for making a *prima facie* case of obviousness.

However, we direct the examiner's attention to the numerous difficulties encountered in making and expressing recombinant DNA sequences encoding chimeric antibodies when the starting material is the mere disclosure of the existence of a monoclonal antibody. See pp. 8-18 of the Appellants' Brief. The examiner has alleged that it would have been obvious to "deduce the DNA sequence of the variable region of the antibody,"[5] without any explanation (or evidence) as to how this is to be done from the teachings of the Bumol publications. In our opinion, *on these facts*, at a minimum, the 9.2.27 DNA sequence, or a fragment thereof, or the 9.2.27 amino acid sequence, or a fragment thereof, must be available as the starting material before one skilled in the art would have a reasonable expectation of success in making a chimeric DNA sequence which comprises the 9.2.27 variable region. On these facts, we do not find that the mere disclosure of the existence of a protein provides one of ordinary skill in the art a reasonable expectation of successfully deducing the DNA sequence of said protein, let alone the construction of additional compositions comprising all or a portion of said DNA sequence.

[5] *Ibid.*, p. 4, lines 13-15.

The decision of the examiner is reversed.

REVERSED

FRED E. McKELVEY
Chief Administrative
Patent Judge

SHERMAN D. WINTERS
Administrative Patent Judge

JOAN ELLIS
Administrative Patent Judge

BOARD OF PATENT
APPEALS
AND
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Appeal No. 93-3731
Application 07/387,665

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APPENDIX

1. A recombinant DNA compound that comprises a DNA sequence encoding the light chain variable region of a chimeric monoclonal antibody, the DNA sequence coding for an amino acid sequence comprising:

Asn-Ile-Val-Leu-Thr-Gln-Ser-Pro-Ala-Ser
Leu-Ala-Val-Ser-Leu-Gly-Gln-Arg-Ala-Thr
Ile-Ser-Cys-Arg-Ala-Ser-Glu-Ser-Val-Asp
Ser-Tyr-Gly-Asn-Ser-Phe-Met-His-Trp-Tyr
Gln-Gln-Lys-Pro-Gly-Gln-Pro-Pro-Lys-Leu
Leu-Ile-Tyr-Leu-Ala-Ser-Asn-Leu-Glu-Ser
Gly-Val-Pro-Ala-Arg-Phe-Ser-Gly-Ser-Gly
Ser-Arg-Thr-Asp-Phe-Thr-Leu-Thr-Ile-Asp
Pro-Val-Glu-Ala-Asp-Asp-Ala-Ala-Thr-Tyr
Tyr-Cys-Gln-Gln-Asn-Asn-Glu-Asp-Pro-Leu
Thr-Phe-Gly-Ser-Gly-Thr-Lys-Leu-Glu-Ile
Lys-Arg.

17. The recombinant DNA compound that comprises a DNA sequence encoding the heavy chain variable region of a chimeric monoclonal antibody, the DNA sequence coding for an amino acid sequence comprising:

Gln-Val-Gln-Leu-Gln-Gln-Ser-Gly-Pro-Glu
Leu-Val-Lys-Pro-Gly-Ala-Ser-Val-Lys-Ile
Ser-Cys-Lys-Ala-Ser-Gly-Tyr-Ala-Phe-Ser
Arg-Ser-Trp-Met-Asn-Trp-Val-Lys-Gln-Arg
Pro-Gly-Gln-Gly-Leu-Glu-Trp-Ile-Gly-Arg
Ile-Tyr-Pro-Gly-Asp-Gly-Asp-Thr-Asn-Tyr
Asn-Gly-Lys-Phe-Lys-Gly-Lys-Ala-Thr-Leu
Thr-Ala-Asp-Lys-Ser-Ser-Ser-Thr-Ala-Tyr
Met-Gln-Val-Ser-Ser-Leu-Thr-Ser-Val-Asp
Ser-Ala-Val-Tyr-Phe-Cys-Ala-Arg-Gly-Asn
Thr-Val-Val-Val-Pro-Tyr-Thr-Met-Asp-Tyr
Trp-Gly-Gln-Gly-Thr-Ser-Val-Thr-Val-Ser
Ser.